HFA 305 (Dockets Management Branch)

1269 '02 DEC 23 P12:58

Approval Date: SEP 27 2002

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-346

Trenbolone Acetate and Estradiol (COMPONENT® TE-H)

For increased rate of weight gain and improved feed efficiency for heifers fed in confinement for slaughter.

Sponsored by:

Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214

FREEDOM OF INFORMATION SUMMARY

Component® TE-H Ear Implant for Heifers Fed in Confinement for Slaughter

1. GENERAL INFORMATION

a. File Number:	ANADA 200-346
b. Sponsor:	Ivy Laboratories Division of Ivy Animal Health, Inc. 8857 Bond Street Overland Park, KS 66214 Drug Labeler Code: 021641
c. Established Names:	Trenbolone acetate and estradiol
d. Propriety Names:	Component® TE-H
e. Dosage Form:	Implantation (ear implant) as per 21 CFR 522.2477.
f. How Supplied:	As an implant made up of 7 pellets with each pellet containing 20 mg trenbolone acetate and 2 mg estradiol
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	Trenbolone acetate: 140 mg trenbolone acetate activity. Estradiol: 14 mg estradiol activity.
i. Route of Administration:	Subcutaneous ear implant
j. Species/Class:	Heifers fed in confinement for slaughter
k. Recommended Dosage:	One implant containing 140 mg trenbolone acetate and 14 mg estradiol per animal.
l. Pharmacological Category:	Steroid hormone
m. Indications:	For increased rate of weight gain and improved feed efficiency for heifers fed in confinement for slaughter.

n. Pioneer Product: Revalor®-H
Trenbolone acetate and estradiol
NADA 140-992
Intervet.

2. EFFECTIVENESS

The abbreviated new animal drug application for Component® TE-H contains adequate data from a well-controlled investigation demonstrating bioequivalence of Component® TE-H to the parent drug, Revalor®-H. The bioequivalence study was conducted in a major beef producing area of the United States.

Materials and Methods:

Name and Address of Investigator:

Tony Janes, B.S.
CAVL, Inc.
9602 South Washington
Amarillo, TX 79118

The purpose of the study was to demonstrate bioequivalence of Component® TE-H to Revalor®-H through comparison of blood serum trenbolone-17β and estradiol-17β parameters in steers implanted with Component® TE-H and Revalor®-H.

One hundred ten steers were used as test animals in a 91 day study. Steers were used to eliminate the effects of endogenous estradiol from the ovary. Animals were housed in a single pen. Steers weighed between 508 and 581 lbs when the study was initiated. Component® TE-H and Revalor®-H were administered subcutaneously in the middle third of the ear with the respective implanting device. Cattle were weighed on Day 0 to serve as an initial weight and subsequently on Days 49 and 91 to monitor weight gain of the animals.

Blood samples were collected from Day -2 through Day 91 of treatment at regular predetermined intervals to monitor serum levels of trenbolone-17β and estradiol-17β by radioimmunoassay. Samples were collected on days -2, -1, 0 3, 5, 7, 9, and every 7 days from days 14 to 91.

Trenbolone-17β and estradiol-17β concentrations (pg/ml) for sample time periods were evaluated in two replicates. The natural log of the area-under-the-curve (log AUC)and the natural log of the maximum observed drug concentration (log CMAX) are identified as pivotal variables for extent of product bioavailability and rate of absorption, respectively, in "Guidance for Industry #35: Bioequivalence" (Docket No. 94D-0401, 2000). However, because implants have an extended duration of drug release with no single, clearly defined peak for determination of CMAX, alternative procedures were chosen. The log AUC for days

0 to 91 (extent of product bioavailability)and the natural log of partial areas-under-the-curve (rate of absorption) were used as pivotal variables for bioequivalence determination. The partial area-under the curve variables were: natural log of the area-under-the-curve from day 0 to day 14 (log AUC1), natural log of area-under-the-curve from day 14 to day 56 (log AUC2), and natural log of area-under-the-curve from day 56 to day 91 (log AUC3). The partial areas (log AUC1, log AUC2 and log AUC3) were calculated from the mean of the sample time replicates.

Log AUC, log AUC1, log AUC2 and log AUC3 were analyzed using a completely random design. Endpoints for establishing bioequivalence for log AUC1, log AUC2 and log AUC3 were calculated to adjust for both the correlation between the treatment differences for the three areas and the use of three variables (areas) in the establishment of bioequivalence. The bioequivalence bounds for log AUC were -20% to +25% of the pioneer product at the 90% confidence level. Bioequivalence bounds of the partial areas were -25% to +33% of the pioneer product at the 90% confidence level.

Results:

The analysis of pivotal variables related to concentrations of Trenbolone-17β and Estradiol-17β, log AUC and three partial areas (log AUC1, log AUC2 and log AUC3), show that Revalor®-H and Component® TE-H are bioequivalent (see Tables 1 and 2). With respect to both Trenbolone-17β (Table 1) and Estradiol-17β (Table 2), the lower and upper limits for log AUC were within the -20% to +25% criterion, while the lower and upper limits for the partial areas (log AUC1, log AUC2 and log AUC3) were within the -25% to +33% criterion.

Conclusions:

Based on the results of this study, we conclude that Revalor®-H and Component® TE-H are bioequivalent.

Table 1. Test of Bioequivalence of Trenbolone-17β Based on log AUC and log AUC1, AUC2 and AUC3

Analysis Variable	LS Mean Component TE-H	LS Mean Revalor-H	Difference	Lower[e]	Upper[e]
LAUC[a]	9.6159	9.602	0.0139	-9.69%	12.89%
LAUC1[b]	8.0104	8.1544	-0.1440	-24.29%	-0.98%
LAUC2[c]	9.0254	8.9350	0.0904	-4.38%	25.33%
LAUC3[d]	8.0601	8.102	-0.0419	-18.17%	12.4%

[a]LAUC = natural log of the area-under-the-curve (days 0-91)
[b]LAUC1 = natural log of the area-under-the-curve (days 0-14)
[c]LAUC = natural log of the area-under-the-curve (days 14-56)
[d]LAUC = natural log of the area-under-the-curve (days 56-91)

[e]Lower and upper required bioequivalence endpoints for Component T-EH were from -20% to +25% of Revalor-H for LAUC and from-25% to +33% for the partial areas (LAUC1, LAUC2 and LAUC3).

Table 2. Test of Bioequivalence of Estradiol-17β Based on log AUC and log AUC1, AUC2 and AUC3

Analysis Variable	LS Mean Component TE-H	LS Mean Revalor-H	Difference	Lower[e]	Upper[e]
LAUC[a]	8.2599	8.2289	0.0310	6.69%	14.03%
LAUC1[b]	6.3015	6.2589	0.0426	-9.99%	20.99%
LAUC2[c]	7.6194	7.4659	0.1535	3.44%	31.40%
LAUC3[d]	7.0561	7.1941	-0.1380	-24.86%	1.00%

[a]LAUC = natural log of the area-under-the-curve (days 0-91)
[b]LAUC1 = natural log of the area-under-the-curve (days 0-14)
[c]LAUC = natural log of the area-under-the-curve (days 14-56)
[d]LAUC = natural log of the area-under-the-curve (days 56-91)

[e]Lower and upper required bioequivalence endpoints for Component T-EH were from -20% to +25% of Revalor-H for LAUC and from-25% to +33% for the partial areas (LAUC1, LAUC2 and LAUC3).

3. TARGET ANIMAL SAFETY AND EFFECTIVENESS

Under the provisions of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Action (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

4. HUMAN SAFETY

- Allowable Incremental Increases and Tolerances for Residues:

  The allowable incremental increases established for the pioneer product apply to the generic product. Estradiol is regulated under 21 CFR 556.240. No residues of estradiol, resulting from the use of estradiol or any of the related esters, are permitted in the uncooked edible tissues of heifers in excess of the following increments above the concentrations of estradiol naturally present in untreated animals: 120 ppt for muscle, 240 ppt for liver, 360 ppt for kidney, and 480 ppt for fat.

  The tolerances established for the pioneer product apply to the generic product. Trenbolone acetate is regulated under 21 CFR 556.739. The Acceptable Daily Intake (ADI) for total residues of trenbolone is 0.4 micrograms per kilogram body weight per day. A tolerance for trenbolone residues in uncooked edible tissues of cattle is not needed.

- Withdrawal Time:

  When a generic product demonstrates bioequivalence to the pioneer product in a blood level study where the duration of the study exceeds the withdrawal time assigned to the pioneer product, the generic product is assigned the withdrawal time established for the pioneer product. The zero withdrawal is established for implants containing trenbolone acetate and estradiol.

- Regulatory Method for Residues:

  A regulatory method is not required.

5. AGENCY CONCLUSIONS

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that the trenbolone acetate and estradiol (Component® TE-H), when used under its proposed conditions of use, is safe and effective for its labeled indications.

6. ATTACHMENTS

Facsimile Generic Labeling and Currently Approved Pioneer Labeling are attached as indicated below:

Box Label (Generic)
Foil Pouch Label (Generic)
Package Insert (Generic)
Box Label (Pioneer)
Cartridge Label (Pioneer)
Package Insert (Pioneer)

RESTRICTED DRUG — USE ONLY AS DIRECTED (CALIFORNIA) — FOR USE IN ANIMALS ONLY
NOT FOR HUMAN USE — KEEP OUT OF REACH OF CHILDREN

Storage Conditions
Store in a refrigerator (2°-8°C; 36°-46°F) and protect from sunlight.
Use before the expiration date.

COMPONENT® TE-H

BRAND IMPLANTS

FOR HEIFERS
fed in confinement for slaughter

trenbolone acetate 140 mg and estradiol USP 14 mg

VetLife

COMPONENT TE-H contains trenbolone acetate and estradiol for increased rate of weight gain and improved feed efficiency in a slow-release delivery system.

Contains: 5 Cartridge Belts* of 20 implants each. Each dose consists of trenbolone acetate 140 mg and estradiol USP 14 mg.

Manufactured by a non-sterilizing process.

* Patented by Ivy Animal Health, Inc. ANADA 200-346, Approved by FDA

100 IMPLANTS

FPO

6 13562 03205 3

TAKE TIME
OBSERVE LABEL DIRECTIONS

WARNING: Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 7 pellets (entire contents of one cartridge) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food.

Note: Studies have demonstrated that the administration of COMPONENT® TE-H can result in decreased marbling scores when compared to non-implanted heifers.

Important: Read the enclosed instruction brochure. Use as illustrated with a CAREFUL CLEAN TECHNIQUE. Never take short cuts at the expense of CLEANLINESS.

COMPONENT is a registered trademark of Ivy Laboratories.

Manufactured for **VetLife** by Ivy Laboratories • Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.

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COMPONENT® TE-H
trenbolone acetate 140 mg
and estradiol USP 14 mg
FOR HEIFERS
fed in confinement for slaughter

COMPONENT® TE-H

BRAND IMPLANTS

FOR HEIFERS
fed in confinement for slaughter

trenbolone acetate 140 mg and estradiol USP 14 mg

VetLife®

TEAR H

COMPONENT TE-H contains trenbolone acetate and estradiol USP for increased rate of weight gain and improved feed efficiency in a slow-release delivery system.

Contains: One Cartridge Belt* of 20 implants sealed in a sanitary foil pouch. Each dose consists of trenbolone acetate 140 mg and estradiol USP 14 mg.

Manufactured by a non-sterilizing process.

* Patented by Ivy Animal Health, Inc. ANADA 200-346, Approved by FDA

One 20-Dose Cartridge Belt

TEAR HERE

WARNING: Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 7 pellets (entire contents of one cartridge) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food.

RESTRICTED DRUG — USE ONLY AS DIRECTED (CALIFORNIA) — FOR USE IN ANIMALS ONLY
NOT FOR HUMAN USE — KEEP OUT OF REACH OF CHILDREN

Note: Studies have demonstrated that the administration of COMPONENT® TE-H can result in decreased marbling scores when compared to non-implanted heifers.

Important: Read the enclosed instruction brochure. Use as illustrated with a CAREFUL CLEAN TECHNIQUE. Never take short cuts at the expense of CLEANLINESS.

Storage Conditions: Store in a refrigerator (2°-8°C; 36°-46°F) and protect from sunlight. Use before the expiration date.

COMPONENT is a registered trademark of Ivy Animal Health, Inc.
Manufactured for **VetLife** by Ivy Laboratories • Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.
01 07 02 00

PURCHASE SEAL 20 IMPLANTS

6 13562 03110 0

EXP

LOT

COMPONENT®
BRAND IMPLANTS

VetLife

TE-H

FOR HEIFERS
fed in confinement for slaughter

trenbolone acetate 140 mg and
estradiol USP 14 mg

20 dose CARTRIDGE BELT*

For use with the COMPONENT One Gun®**
For Use in Animals Only

Each CARTRIDGE BELT holds 20 doses of COMPONENT® TE-H Implants. Each dose of 7 pellets consists of 140 mg of trenbolone acetate and 14 mg estradiol USP. COMPONENT® TE-H Implants are recommended for use in heifers fed in confinement for slaughter for INCREASED RATE OF WEIGHT GAIN AND IMPROVED FEED EFFICIENCY.

Manufactured by a non-sterilizing process.

INDICATIONS FOR USE: This product contains trenbolone acetate and estradiol for increased rate of weight gain and improved feed efficiency in a slow-release delivery system.

NOTE: Studies have demonstrated that the administration of COMPONENT® TE-H can result in decreased marbling scores when compared to non-implanted heifers.

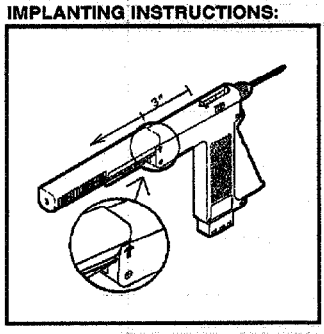
GENERAL INSTRUCTIONS: Study the instructions which should be followed carefully at all times, avoiding short cuts. Skin infection can be avoided by properly preparing implant site and implanter. During fly season use fly repellent on implant site. One designated team member should always do the implanting. Cleanliness of hands and instruments is important at all times.

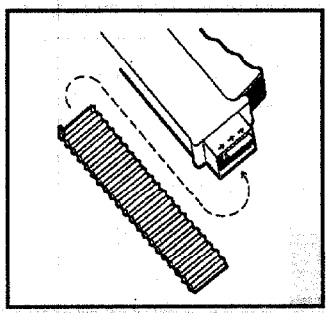
WARNING

Not to be used in animals intended for subsequent breeding, or in dairy animals. Implant one dose — 7 pellets (entire contents of one cartridge) — in the ear subcutaneously. Any other site of implantation is in violation of Federal Law. DO NOT attempt to salvage implantation site for animal feed or human food.

RESTRICTED DRUG — USE ONLY AS DIRECTED (CALIFORNIA) — FOR USE IN ANIMALS ONLY — NOT FOR HUMAN USE — KEEP OUT OF REACH OF CHILDREN

IMPLANTING INSTRUCTIONS:



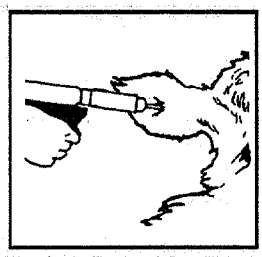


Loading the Implanter
Load the Implanter following the instructions supplied with each implanter.

Restrain the Animal
Speed of implantation as well as safety of handlers is best achieved by restraining animal in a squeeze chute using head restraint. When implanting horned cattle, better control is obtained with additional use of nose tongs.

Prepare the Implant Site
Scrub the back side of the ear (implant site) with a piece of clean absorbent cotton which has been soaked with topical germicidal solution. Follow manufacturer's directions on germicide for correct strength and preparation of solution. Avoid getting in animal's eyes.

Where to Implant
The full contents of the cartridge (all 7 pellets) should be implanted beneath the skin on the back side of the middle one-third of the ear as illustrated in the drawing. **The implant must not be closer to the head than the edge of the auricular cartilage ring farthest from the head.** The location for insertion of the needle is a point toward the tip of the ear at least a needle length away from the intended deposition site. Avoid injuring the large arteries, veins and cartilage of the ear.



Insert the Needle
With one hand firmly grasp the ear. With the other hand insert needle point through the skin and ease forward on a lateral plane until the entire length of the needle is under the skin.

Implant the Pellets
After inserting the needle fully in the correct implant position, squeeze the trigger fully. As the needle is withdrawn from the ear, the controlled-pressure plunger action properly deposits the implant in the needle track. This procedure should prevent breakage or crushing of pellets if otherwise forced into contact with tough fibrous-tissue underlying the skin. The length and total contact area of a single dose are designed to permit absorption of the hormones after implantation to stimulate good weight gain. Broken or crushed pellets may interfere with rates of gain.

Clean the Needle
Clean the implanter needle with alcohol or a properly diluted germicidal solution prior to implanting the next animal.

Storage Conditions
Store in a refrigerator (2°-8°C; 36° to 46° F) and protect from sunlight.
Use before the expiration date printed on foil pouch.

ANADA 200-346, Approved by FDA

*U.S. Patent No. 4,531,938
**U.S. Patent Nos. 4,762,515 & 5,522,797 – Ivy Animal Health, Inc.

Manufactured for **VetLife** by Ivy Laboratories.
Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.

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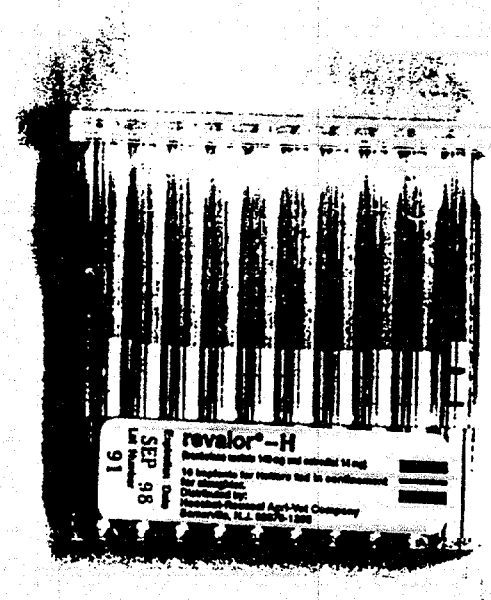
Pioneer Label - revalor®-h
10 Dose Cartridge Label



Pioneer Label - revalor®-h
100 Dose Carton (Front)

NDC 12799-810-07

revalor®–h

(trenbolone acetate and estradiol)

FOR HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

Box of 10 x 10 Cartridge Implants

Hoechst
Roussel

Pioneer Label - revalor®-h
100 Dose Carton (Top)

revalor®–h

(trenbolone acetate and estradiol)

FOR HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

Box of 10 x 10 Cartridge Implants

Hoechst
Roussel

Pioneer Label - revalor®-h
100 Dose Carton (Left Side)

[redacted]

PACKAGE QUANTITIES
Box of 10 x 10 cartridge implants.
Contains 100 doses in ten cartridges with ten implants per cartridge. each dose contains 7 small yellow pellets. Each pellet contains 20 mg of trenbolone acetate and 2 mg estradiol.

STORAGE CONDITIONS:
Store in a refrigerator (2-8°C; 36-47°F) and protect from sunlight. Use before the expiration date printed on the box and on the cartridge.

INDICATIONS FOR USE
This product contains trenbolone acetate and estradiol for increased rate of weight gain and improves feed efficiency in a slow-release delivery system.

NOTE
Studies have demonstrated that the administration of revalor®-h can result in decreased marbling scores when compared to non-implanted heifers.

Pioneer Label - revalor®-h
100 Dose Carton (Right Side)

Expiration Date : SEP 98

Lot Number : 91

[redacted]

USE DIRECTIONS
See enclosed package insert.

WARNING
Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only.
Not for Use in Humans. Implant pellets in the ear only.
Any other location is in violation of Federal Law.
Do not attempt salvage of implanted site for human or animal food.

Made in France by:
Roussel Uclaf
Division agro-veterinaire

481007-11/94

Distributed by:
Hoechst-Roussel Agri-Vet Co.
Route 202-206 North
Somerville, NJ 08876-1258
USA

Pioneer Label - revalor®-h
Package Insert - (Front)

and improved feed efficiency in a slow-release delivery system.

NOTE

Studies have demonstrated that the administration of Revalor®H can reslut in decreased marbling scores when compared to non-implanted heifers.

DOSAGE

Dosage Form:

One implant containing 140 mg trenbolone acetate and 14 mg estradiol is administered to each animal. The 7 pellets which make up the dosage of Revalor®-H are contained in one division of the multiple dose cartridge. Ten doses are in each cartridge. The cartridge is designed to be used with a special implant gun.

Route of Administration:

The implant is placed under the skin on the posterior aspect of the ear by means of a special implanter available from Hoechst-Roussel Agri-Vet Co.

With the animal suitably restrained, the skin on the outer surface of the ear should be cleaned. The im-plant is then administered by the method shown in the diagram below.

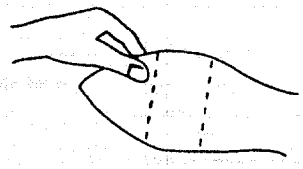


Fig. 1 - Ear of Bovine Ready for implantation

SITE OF IMPLANTATION

After appropriately restraining the animal to allow access to the ear, cleanse the skin at the implant needle puncture site. It is subcutaneous between the skin and cartilage on the back side of the ear and below the midline of the ear.

The implant must not be placed closer to the head than the edge of the cartilage ring farthest from the head. The location of insertion of the needle is a point toward the tip of the ear and at least a needle length away from the intended deposition site. Care should be taken to avoid injuring the major blood vessels or cartilage of the ear.

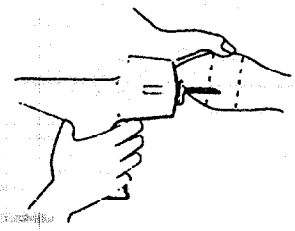


Fig. 2 - Rear View of the Bovine Ear Showing the Site for insertion of the implanter Needle

METHOD OF USE

1. Do not remove the cap of the cartridge containing the implants.
2. Place the cartridge (D) (with the capped end to the front) into slot at the top of the implanter magazine (marked A on the diagram).

revalor®h

(trenbolone acetate and estradiol)

FOR HEIFERS
FED IN CONFINEMENT
FOR SLAUGHTER

DESCRIPTION

Revalor®-H is an implant con
taining 140 mg of trenbolon
acetate and 14 mg estradiol
Each implant consists of 7 sma
yellow pellets. Ten implants ar
provided in a cartridge.

INDICATIONS FOR USE

This product contains trenbolo
ne acetate and estradiol fo
increased rate of weight gai

Pioneer Label - revalor®-h
Package Insert - (Back)

3. Gently push the cartridge into the slot until it clicks into place.
4. The implanter is then ready for use.
5. Take the ear of the animal firmly with the free hand (in the manner shown in Fig. 2). Then insert the needle into the subcutaneous tissue at the point indicated (in Fig. 2).
6. After inserting the needle to its full extent, squeeze the trigger gradually. Allow the pellets of the implant to be deposited in a single row.
7. Withdraw the implanter. This will advance the cartridge one groove in the magazine and the next implant is now ready for use.
8. When all the implants have been administered, the cartridge will fall out the bottom of the magazine and may be replaced by a new one.
9. To change the needle, loosen the needle locking nut (labelled F in Fig. 3) and replace the needle. Tighten the nut finger tight and the implanter is ready for use.

A - Magazine aperture
B - Needle
C - Cartridge cap
D - Cartridge
E - Trigger
F - Needle locking nut

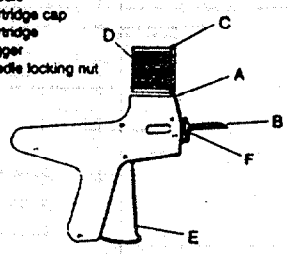


Fig. 3 - Diagram of the Implanter and Cartridge

WARNING

Not to be used in animals intended for subsequent breeding, or in dairy animals.
For Animal Treatment Only.
Not for Use in Humans.
Implant pellets in the ear only
Any other location is in violation of Federal Law.
Do not attempt salvage of implanted site for human or animal food.

STORAGE CONDITIONS

Store in refrigerator (2-8°C; 36-47°F) and protect from sunlight. Use before the expiration date printed on the cartridge.

PACKAGE QUANTITIES

Box of 10 x 10 cartridge implants.

NDC 12799-810.07

® Registered trade mark Roussel Uclaf

Made in France by:
Roussel UCLAF

Distributed by:
Hoechst-Roussel
Agri-Vet Co.
Route 202-206
Somerville, NJ 08876

781000-11/94

ROTANOTICE - 041

Hoechst
Roussel

V 71 165 0